Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

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August 11, 2000

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Draft Guidance for Industry on Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis
Docket No. 00D-1307, Vol. 65 *Federal Register* 37396 (June 14, 2000)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders. The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents. Currently, the PRI pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in commenting on the FDA Draft Guidance for the Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis.

Summary of BMS Comments on Guidance

We commend the U.S. FDA for developing guidance on this topic to assist in the development of parathyroid hormone (PTH) products. However, we consider that the Guidance as it is currently written places restrictions on the development of those compounds which are not warranted by the available information.

Specific Comments

While we acknowledge that findings such as the osteosarcomas noted in the previously conducted rodent studies should be investigated thoroughly to determine their relevance to human use of parathyroid hormone products, such relevance is not yet clear. Differences in the skeletal physiology between rodents and humans, notably the fact that growth plates in rodents remain active into adulthood, suggest that these findings may not be relevant to humans. Osteosarcomas in humans usually occur at active growth plates, and thus are unlikely to occur in adults eligible for treatment with a treatment for osteoporosis. The draft Guidance states within Section IV. CLINICAL STUDIES that the recommended limitation on clinical studies to patients with established disease (as defined by the presence of a fracture and lumbar or hip T-score <-2.5) is included "to improve

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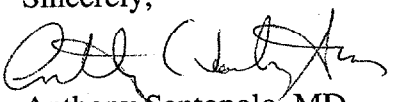
the benefit to risk ratio of PTH". Patients who have not yet experienced an osteoporotic fracture, but who would be considered at significant risk for such an event based on other risk factors, would thus be excluded from investigations of these anabolic agents, though the potential benefit is significant. An assessment of the benefit to risk ratio of such products in a less severe patient population is only possible once the benefit is investigated in clinical trials, so that the preclinical findings mentioned in the guidance can be placed in the proper perspective.

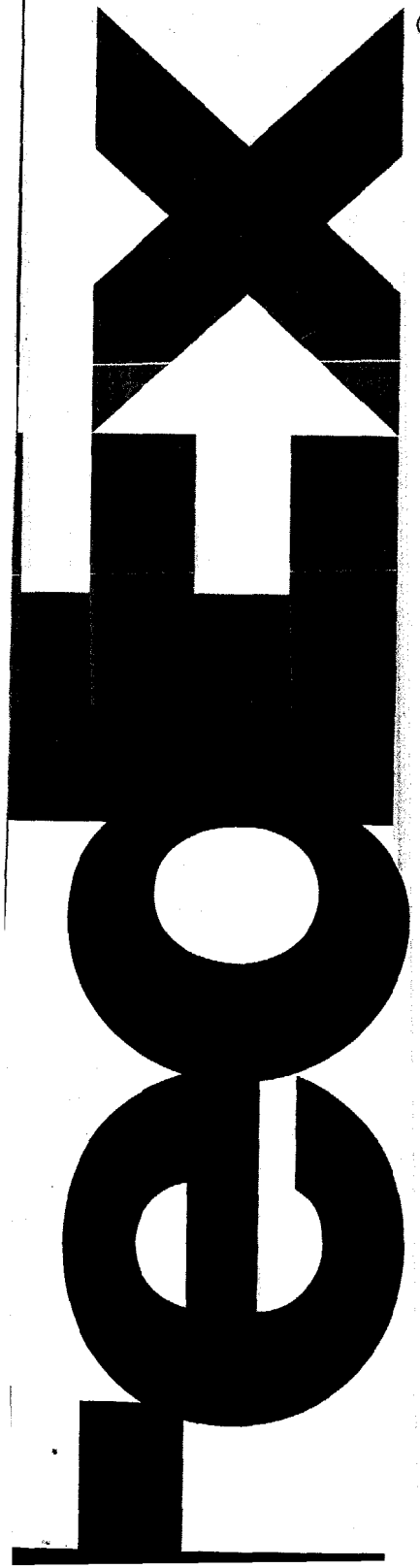
BMS considers that the recommendations in the draft Guidance regarding exclusion of pagetic patients, and those regarding patient follow up and informed consent, to be a prudent response to the findings of the preclinical trials with PTH. However, since limitation of clinical trials to patients with severe osteoporosis does not improve the benefit to risk ratio of PTH products, we recommend that the first paragraph under Section IV. CLINICAL STUDIES be deleted.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,



Anthony Santopolo, MD
Vice-President
Regulatory Policy and External Alliance



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